446

Biomarkers of Extracellular Matrix Remodeling in Chronic GVHD

Carrie L. Kitko [1], Rima Saliba [2], Sung Won Choi [1], Pavan Reddy [3], Steven C. Goldstein [3], John Magenau [3], Attaphol Pawarode [3], Maggi Kennel [3], John E. Levine [1], Eric White [4], Daniel R. Couriel [3]. [1] Pediatric Blood and Marrow Transplant Program, University of Michigan; [2] Stem Cell Transplantation, MD Anderson Cancer Center, Houston, TX; [3] Adult Blood and Marrow Transplant Program, University of Michigan; [4] Pulmonary and Critical Care, University of Michigan, Ann Arbor, MI

Chronic GVHD (cGVHD) is the most important long-term complication of allogeneic transplantation (HCT). It evolves from immune-mediated inflammation to fibrogenesis, resulting in end organ damage such as sclerotic skin and bronchiolitis obliterans syndrome. Thus, biomarkers of extracellular matrix (ECM) remodeling and fibrosis may provide insight into the biology of the disease and contribute to diagnosis and outcome prediction. In order to identify promising candidates, we conducted a discovery experiment in 112 adult patients (median age 52.5 y, range 18-68) with new onset cGVHD. Median time to onset of cGVHD was 165 d (range 37-547) post-HCT. Overall NIH severity at onset was mild (n=16, 14%), moderate (n=53, 47%) or severe (n=43, 39%). The majority of patients had at least one overlap feature (elevated liver enzymes, erythematous rash or GI symptoms; 80%). Plasma samples were obtained at the time of cGVHD onset, biomarkers were assayed simultaneously using a lab-derived (non-commercial) Luminex bead-based assay, and levels of each analyte (assessed by deciles) that provided the best discrimination with survival were determined. Levels of 3 profibrotic proteins (CCL2, IGF-1, IL-13Rα) significantly correlated with TGF-β levels. Of these, TGF-β provided the strongest association with outcomes 1 y post-onset of cGVHD. Patients with low TGF-β ($\leq$ 10 pg/ml; n=36) were 3 times more likely to relapse (Cumulative Incidence (CI) 17% vs 5%,P = .05) and 4 times more likely to experience NRM (CI 23% vs 5%,P = .01) than patients with high TGF-β ($>$ 10 pg/ml; n=76). These increases resulted in lower progression free survival (PFS 60% vs 89%,P = .001) and overall survival (OS 72% vs 92%,P = .01). Low TGF-β was also significantly correlated with the following features at onset: low performance status (P = .01), platelet $<$ 100K (P = .01), and NIH lung 2/3 (P = .01). However, the impact of low TGF-β on OS and PFS was independent of each of these factors when assessed in bivariate analysis. There was no correlation with TGF-β levels and other characteristics such as patient age, diagnosis, high risk disease at HCT, donor type, overall NIH score or progressive onset cGVHD. Patients in the high TGF-β group and high IL-13 group ($>$200 pg/ml) were more likely to later develop sclerotic skin (n=20) (TGF-β 80% vs 65%,P = .1; IL-13 85% vs 62%,p=0.04). On the other hand, low level MMP2 ($\leq$ 5000 pg/ml), an antifibrotic metalloproteinase, were more likely to develop sclerotic cGVHD (50% vs 21%,P = .007). These results suggest ECM turnover is active at the time of cGVHD onset, even prior to the development of clinically apparent sclerosis. Further investigation of factors that impact the balance and transition between inflammation and fibrosis may provide a better understanding of the pathophysiology and new biomarker opportunities for cGVHD.

447

Non-Relapse Mortality in Chronic Graft Versus Host Disease: Risk Factors At Onset and Reponse to Treatment

Carrie L. Kitko [1], Rima Saliba [2], Sophie Paczesny [1], Maggi Kennel [3], Sung Choi [4], Pavan Reddy [3], John Levine [1], Daniel R. Couriel [3]. [1] Pediatric Blood and Marrow Transplant Program, University of Michigan; [2] Stem Cell Transplantation, MD Anderson Cancer Center, Houston, TX; [3] Adult Blood and Marrow Transplant Program, University of Michigan; [4] Blood and Marrow Transplant Program, University of Michigan, Ann Arbor, MI

Chronic graft versus host disease (cGVHD) is a major contributor to morbidity and mortality in long-term survivors of allogeneic hematopoietic cell transplantation (HCT). The treatment course is heterogeneous and unpredictable, and a prognostic system at the time of disease onset is highly desirable. We developed a simple system that should minimize inter-provider variability, and can be applied at disease onset. We studied 341 consecutive adult patients (age 18-71y; median 53y) who received HCT at the University of Michigan from 2007 to 2010. Data was prospectively collected under an IRB approved protocol. Cumulative incidence of cGVHD was 47%, with a median time to onset of 190d (range 37-806d). We performed univariable analysis on multiple potential risk factors (RF) for non-relapse mortality (NRM), with relapse as a competing risk (Table 1). History of severe acute GVHD grades III/IV (severe aGVHD) (Hazard Ratio (HR)=4.0, $P < .001$), Karnofsky performance score (KPS) $\leq$ 70% (HR 4.6, $P < .001$), and grade 2/3 lung (HR=3.3,P = .04) were the strongest predictors of NRM, while presence of grade 1 liver cGVHD was protective (HR=0.3,P = .03). The simplest stratification grouped patients into 3 categories: High risk (KPS $\leq$ 70% and/or severe aGVHD), low risk (grade 1 liver, without high risk features), and intermediate risk (all others). Four year NRM in our model was 52% in high risk (n=44, ref), 4% in low risk (n=28,P = .01), and 18% in intermediate patients (n=86,P = .001). Within the high risk group, both low KPS and prior severe aGVHD remained independent predictors after adjustment for each other (HR=4.5,P = .02 and HR=3.4,P = .02, respectively), and in the entire cohort. Low KPS patients were more likely to have lung involvement, be on steroids, and have more severe cGVHD, implying that KPS serves as a composite of multiple other RF, including both HCT-related morbidities and cGVHD burden. In addition to KPS and history of severe acute GVHD, lack of response 1 month after the initiation of therapy was independently predictive of NRM in 141 treated patients (HR= 3.1, 95% CI 1.3-7.4, $P < .01$). If validated in an independent population, this classification system may be clinically useful and facilitate referral and management in chronic GVHD clinics.

Table 1

Risk Factor	Univariable			
	n	HR	95% CI	*P* value
Before Onset				
Age at HCT, y				
18-40	29	Ref		
41-55	70	1.8	0.5-6.4	0.3
$>$ 55	59	2.3	0.7-8.05	0.2
Related donor	79	0.6	0.3-1.2	0.2
Reduced Intensity Conditioning	51	1.1	0.5-2.4	0.7
History of aGVHD III-IV	20	4.0	1.9-8.5	$<$ .001
Onset				
Karnofsky Performance Score $\leq$ 70%	31	4.6	2.5-9.5	$<$ .001
NIH Onset Severity				
Mild	23	Ref		
Moderate	79	0.6	0.2-1.8	0.4
Severe	56	1.2	0.4-3.4	0.7
Progressive onset vs De novo/Quiescent	34	2.1	1.0-4.5	0.05
Platelets $<$ 100,000/mm^3 at onset	42	1.4	0.7-3.1	0.3
On steroids at onset	28	2.0	0.9-4.5	0.09
NIH grade 1 liver at onset	40	0.3	0.1-0.9	0.03
NIH grade 2/3 lung at onset	17	3.3	1.03-10.3	0.04